

REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

I. Claim Status and Amendments

Claims 1-22 and 43-51 presently appear in this case. Claims 23-42 were previously cancelled.

Claims 4-17 and 43-51 were withdrawn as non-elected subject matter.

Claims 1-3 and 18-22 were examined on the merits and stand rejected.

Applicants have amended the claims to address the formal matters raised in the Office Action. In particular, claim 1 has been amended to specify that the diastereomeric peptide consists of from 7 to 50 amino acid residues corresponding to an amino acid sequence of a transmembrane domain of a transmembrane protein. Claim 1 has been further amended to specify that the diastereomeric fragment, diastereomeric derivative, and diastereomeric analog comprise at least seven hydrophobic amino acid residues, wherein the derivative and analog comprises at least one conservative amino acid substitution. Support can be found throughout the disclosure in general and original claim 1. See, for instance, paragraph [0072] of Patent Application Publication

No. 2008-0096809 A1 (which corresponds to the instant application).

Minor editorial revisions have been made to the claims to better conform to U.S. claim form and practice. Such revisions are non-substantive and not intended to narrow the scope of protection. For instance, claim 3 is amended to recite "a viral protein, a bacterial protein, an ion channel, a receptor, a transporter, and a pump" to use proper grammar and to provide proper antecedent basis for the "the bacterial protein" of claim 18 (which depends on claim 3). In keeping with US law, the use of "a" or "an" in patent parlance carries the meaning of "one or more". Also, claim 22 is revised to conform with US practice for antecedent basis by reciting ". . . the membrane binding diastereomeric peptide according to claim 1."

Claim 19 has been amended to specify that the transmembrane protein is aspartate Tar receptor and the transmembrane domain comprises the amino acid sequence set forth in SEQ ID NO: 20. Support can be found in original claim 19.

Claim 21 has been amended to correct a typographical error.

No new matter has been added.

On page 2 of the Office Action, the Examiner maintained the Restriction Requirement and stated that "Applicants argue that the present invention discloses that the recognition between a transmembrane domain and a peptide within the cell membrane is not essential".

Applicant wishes to point out that the Examiner has erred in his characterization of Applicant's traversal to the Restriction Requirement in the last response. Applicant maintains that the recognition between the transmembrane domain and the peptide is indeed essential, but that the secondary structure of the peptide is not essential for the interaction of the peptide with the transmembrane domain (page 4, lines 17-22 of the International Application Publication No. WO 2005/060350, which corresponds to priority application PCT/IL04/01157). Applicant notes that the present case relates only to diastereomeric peptides, as well as to diastereomeric fragments, diastereomeric derivatives, and diastereomeric analogs thereof (page 14, lines 29-30, page 15, line 31 of WO 2005/060350). The requirement that the peptide comprises at least two amino acid residues in the D-configuration is explicitly disclosed throughout the specification (e.g., page 4, line 1, line 8, lines 12-16, line 23; page 5, lines 13-14; and page 12, lines 3-7 of 2 of WO 2005/060350). Based on such, Applicant respectfully disagrees with the Examiner's

statement that "the claims are drawn to analogs and derivatives which are taught by the art" (page 2 of the Office Action). Nonetheless, to further clarify the essence of the present invention, claim 1 has been amended to recite diastereomeric fragments, diastereomeric derivatives, and diastereomeric analogs.

II. Information Disclosure Statement

The Examiner is correct in stating that US 6,133,413, as cited in the previous Information Disclosure Statement (IDS), is to Mouri et al. and not Bolognesi et al. Accordingly, Applicant has concurrently filed herewith an IDS with the correct reference citation to ensure that the correct information is listed on the face of a patent issuing from this application. It is believed that no fee is required for submitting this IDS, since the reference has already been considered and discussed by the Examiner. Nonetheless, the Office is requested to kindly return an Examiner-initialed PTO-1449 form indicating noting official consideration of the reference using the correct citation.

III. Priority claim

The Examiner has stated that Applicant has not complied with one or more conditions for receiving the benefit

of earlier filed Application No. 60/530,899 under 35 U.S.C. 119(e). Specifically, the Examiner contends that Application No. 60/530,899 is void of support for claims 18-21, drawn to peptides wherein the bacterial protein is aspartate Tar receptor and to peptides of specific sequences (*i.e.*, SEQ ID NO:20, 22-23). Applicant respectfully traverses this position.

Prior application No. 60/530,899 relates to diastereomeric peptides corresponding to transmembrane domains of membrane proteins. Among the membrane proteins disclosed therein, receptors are explicitly indicated (page 5, lines 20-23 of Application NO. 60/530,899). It must be made clear that the essence of the present case is not transmembrane domains of membrane proteins. The essence of the present invention is the surprising finding that diastereomeric peptides which correspond to known transmembrane domains of membrane proteins can inhibit membrane protein assembly despite the disruption of the helix structure of these diastereomeric peptides. HIV-1_{LAV-1} gp41, Glycophorin A, or Aspartate Tar receptor are provided in this application as examples of such membrane proteins. The sequences of the transmembrane domains of aspartate receptor, Tar-1 and Tar-2, were known at the filing date of Application No. 60/530,899 (See, for example, Melnyk et al., Biochem. 40: 11106-11113, 2001). It is well established that a patent application specification need not

teach, and preferably omits, what is well known in the art. In re Buchner, 929 F.2d 660,661, 18 USPQ 2d 1331, 1332 (Fed. Cir. 1991); see also MPEP § 2164.01. Therefore, it is respectfully submitted that prior application No. 60/530,899 provides adequate support for claims 18-21 of the instant application. Thus, please acknowledge Applicant's priority claim.

IV. Claim Objections

On page 6 of the Office Action, claim 21 was objected for containing an informality. The present amendment overcomes this objection for reasons which are self-evident.

V. Indefiniteness Rejections

On page 6 of the Office Action, claims 1 and 19-21 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite. The Examiner stated that the definition of diastereomeric active fragments is unclear and that although the specification provides a definition for a "diastereomeric peptide", such definition is separate and distinct from derivatives, analogs, and diastereomeric active fragments. This rejection is traversed.

As described in the present application, the term "diastereomeric peptide" refers to a peptide comprising both L-amino acid residues and D-amino acid residues (see page 12,

lines 17-18 of WO 2005/060350). It should be clear that diastereomeric fragments, diastereomeric derivatives and diastereomeric analogs (see page 14, line 29 through page 16 line 21 of WO 2005/060350) are also diastereomeric peptides and as such they also comprise both L-amino acid residues and D-amino acid residues. Therefore, diastereomeric fragments, diastereomeric derivatives and diastereomeric analogs also fall under the definition of diastereomeric peptides as set forth in the disclosure. Nonetheless, Applicants have amended claim 1 in a manner to more clearly define that the fragments, derivatives and analogs are also diastereomeric. Thus, it is believed that the language of amended claim 1 is clear and definite.

The Examiner further stated that the term "active" in claim 1 is a relative term which renders the claim indefinite. For the sole purpose of expediting prosecution and not to acquiesce to the Examiner's position, Applicant removed this term from claim 1.

The Examiner further stated that the scope of analogs and derivatives is unclear and that it is unclear what structural features are required by the analogs and derivatives. Applicant disagrees. It should be noted that the application discloses that the diastereomeric peptides correspond to the amino acid sequence of a transmembrane

domain of a transmembrane protein. The application further discloses that the diastereomeric peptides comprise at least seven amino acid residues which enable the peptides to be incorporated within the membrane, these amino acid residues are hydrophobic amino acid residues (page 5, lines 23-24; page 16, lines 24-30 of WO 2005/060350). To clarify such, Applicants have amended claim 1 to specify that the diastereomeric fragments, derivatives and analogs comprise at least 7 hydrophobic amino acid residues.

The Examiner stated that the scope of claims 19 and 21 is unclear because claim 19 comprises a peptide where Q and S are L-amino acids, while claim 21 states that Q and S are D-amino acids. In order to correct the presumed inconsistency indicated by the Examiner, claim 19 has now been amended to recite that the membrane protein is aspartate Tar receptor and that the transmembrane domain comprises the amino acid sequence set forth in SEQ ID NO: 20. Thus, claim 1, as amended, and claims 19-21 dependent thereon, now include further limitations to overcome this concern.

Based on the above, the claims are believed to be clear, definite and have full antecedent basis. Thus, this rejection is believed to be overcome, and withdrawal thereof is respectfully requested.

VI. Written Description Rejection

Claims 1-3, 18, 22 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons set forth on pages 8-14. The Examiner stated that claims 2-3 include any peptide comprising 7-50 amino acids of the wide range of transmembrane proteins. The Examiner further stated that there is no specific common core for the peptides of claim 18 and that the peptides disclosed in the application are not representative of any and all peptide fragments of the aspartate Tar receptor. This rejection is traversed as applied to the amended claims.

The test for sufficiency of written description is whether the disclosure reasonably conveys to the artisan that the inventor had possession at the time of filing of the subject matter which is claimed. M.P.E.P., Eighth Ed., Rev. 6 (September 2007) at § 2163, I, 2100-159, 1st column, 2nd paragraph.

This test may be satisfied by: (1) a reduction to practice; (2) a reduction to drawings/chemical formulas; (3) a disclosure of relevant identifying characteristics, such as structure or other physical and/or chemical properties, to sufficiently describe the claimed invention in full, clear, concise and exact terms; (4) a disclosure of functional

characteristics coupled with a known or disclosed correlation between function and structure; (5) a sufficient description of a representative number of species; or (6) a combination of the above, sufficient to show the inventors were in possession of the invention. M.P.E.P. (Eighth Ed., Rev. 6 (September 2007) at § 2163,II, A, 3a(i)-(ii).

In the instant case and as noted above, Applicants have amended the claims in a manner believed to overcome this rejection. To start, claim 1 has been amended to "consisting format" and to specify that the diastereomeric peptide corresponds to an amino acid sequence of a transmembrane domain of a transmembrane protein. Thus, in contrast to the Examiner's position, the claims do not refer to any peptide comprising 7-50 amino acids, and the claims now define a core of 7-50 amino acids. Also, claim 18, which depends indirectly upon claim 1, now also recites diastereomeric peptides consisting of 7 to 50 amino acid residues which correspond to the amino acid sequence of a transmembrane domain of a aspartate receptor. Therefore, the claims do not encompass the broad genus as argued by the Examiner. The genus of the amended claims does not include 1-7, 2-8,...501-507 of the aspartate receptor, but rather the transmembrane domains of aspartate receptor, e.g., Tar-1 located at residues 7-30 of aspartate receptor and flanking regions. Moreover, to further

define the diastereomeric derivatives and analogs, claim 1 has been further amended to recite that the diastereomeric derivatives and analogs comprise at least one amino acid substitution, wherein the amino acid substitution is a conservative amino acid substitution.

The Examiner further stated that there is no teaching in the specification regarding what part of the structure can be varied while retaining the ability to bind the transmembrane protein thereby inhibiting functional assembly. The Examiner stated that no common core sequence is taught. Applicants traverse this position. In reply, Applicants again note that independent claim 1, as amended, now specifies that the diastereomeric fragments, analogs and derivatives comprise at least seven hydrophobic amino acid residues, and that the derivatives and analogs comprise at least one amino acid substitution, wherein the amino acid substitution is a conservative amino acid substitution.

Further, it should be noted that the specification provides sufficient guidance along with examples of the claimed peptides. See, for instance, Example 1 in paragraphs [0104] to [0112], which discloses the DP178 diastereomer. Example 2 in paragraphs [0113] to [0117] discloses the HIV-1 Fusion Peptide Diastereomer. Example 3 in paragraphs [0118] to [0119] discloses the Glycophorin-A Diastereomer. Example 4

in paragraphs [0133] to [0142] discloses Hetero-Assembly Between All-L- and a Diastereomer of the Transmembrane Domain-1 of the Aspartate Tar Receptor.

It is respectfully submitted that such disclosure constitutes at least (1) a reduction to practice; (2) a reduction to drawings/chemical formulas; (3) a disclosure of relevant identifying characteristics, such as structure or other physical and/or chemical properties, to sufficiently describe the claimed invention in full, clear, concise and exact terms, to show that Applicants were in possession of the membrane binding diastereomeric peptide of claim 1 at the time of filing. Moreover, the numerous peptides described above and discussed in the examples in the specification are believed to constitute a sufficient description of a representative number of species sufficient to show the inventors were in possession of the membrane binding diastereomeric peptide of the claims.

Therefore, Applicant respectfully submits that the specification provides full written description support for the subject matter of the claims. For this reason, the above written description rejection is believed to be untenable and should be withdrawn.

VII. 101 rejection

Claim 1 has been rejected under 35 U.S.C. 101, because the claimed invention is directed to non-statutory subject matter for the reasons set forth on pages 14-15.

Claim 1 has been amended to "consisting of" format to specify a astereomeric peptide consisting of from 7 to 50 amino acid residues. Therefore, the peptides of the amended claims are not open to peptides longer than 50 amino acids. As such, they do not read on the naturally occurring *E. coli* aspartate receptor. Thus, it is believed that the claims no longer read on a product of nature. Therefore, the rejection should be withdrawn.

VIII. Anticipation Rejection

Claim 1 has been rejected under 35 U.S.C. 102(b) as being anticipated by Melnyk et al., Biochemistry 40: 11106-11113, 2001 (referred to hereafter as "Melnyk") for the reasons on page 15 of the Office Action. The Examiner stated that Melnyk teaches biophysical studies of transmembrane domains of integral membrane proteins, specifically Melnyk teaches the Tar-1 helix as the oligomeric determinant for the Tar protein (abstract of Melnyk). The Examiner further stated that Melnyk teaches the peptide KKK-VVTLLVMVLGVFALLQLISGSLFF-KKK Tar (TM-1), and that the peptide of Melnyk is considered a

derivative/analog as recited in claim 1 because the analogs/derivatives of claim 1 are interpreted as not requiring any D-amino acids. This rejection is traversed.

Melnyk discloses a biophysical study of the transmembrane domains of several integral membrane proteins: epidermal growth factor receptor (EGFR), glycophorin A (GPA), the influenza A virus M2 ion channel (M2), and Tar-1 and Tar-2 of aspartate receptor. Melnyk discloses the peptide KKK-VTLLVMVLGVFALLQLISGSLFF-KKK - the Tar-1 segment.

However, Melnyk does not disclose diastereomeric peptides of the Tar-1 segment as required by the claims. In contrast, the present application discloses diastereomeric peptides only. Moreover, the present application discloses diastereomeric derivatives and diastereomeric analogs only (see, for example, page 4, line 3; page 4, lines 23-25; page 14, lines 29-30; page 15, line 31 of WO 2005/060350). To more clearly distinguish between the derivatives and analogs recited in claim 1 and the peptide of Melnyk, Applicants have amended claim 1 to specify that the derivatives and analogs are diastereomeric derivatives and diastereomeric analogs. As such, the amended claims now clearly directed to "diastereomeric peptides", which as discussed above, is defined as a peptide comprising both L-amino acid residues and D-amino acid residues (see page 12, lines 17-18 of WO

2005/060350). Thus, the claims now require that the analogs and derivatives require D-amino acids, which obviates the basis for the Examiner's rejection, as Melnyk does not disclose such. Since Melnyk does not disclose or suggest each and every element of claim 1 as required for anticipation, Melnyk cannot anticipate claim 1. Thus, the rejection of claim 1 under 35 U.S.C. 102(b) should be withdrawn.

IX. Obvious Rejections

Claims 1-3, 18-22 have been rejected under 35 U.S.C. 103(a) as being obvious over Melnyk and US 5,464,933 to Bolognesi et al. (referred to hereafter as "Bolognesi") and Gerber et al., JMB 322: 491-495 (referred to hereafter as "Gerber") for the reasons set forth on pages 17-21. This rejection is traversed.

Melnyk teaches biophysical studies of transmembrane domains of integral membrane proteins. The Examiner stated that Melnyk does not expressly teach at least 2 D-amino acids in the peptide. The Examiner further stated that Bolognesi teaches peptides which correspond to an HIV transmembrane protein and specifically the incorporation of at least one amino acid residue in a D-isomer configuration into the peptides. The Examiner further stated that Gerber teaches the incorporation of D-amino acids in the peptide and stated that

all-D GPA analogs exhibit the same binding affinities, insertion, and localization as the all L. The Examiner indicated that one of ordinary skill in the art would have had a reasonable expectation of success in producing the membrane binding diastereomeric peptide of claim 1. Applicants disagree.

As indicated above, Melnyk discloses a biophysical study of the transmembrane domains of several integral membrane proteins, specifically of the transmembrane domains Tar-1 and Tar-2 of aspartate receptor. Melnyk discloses that transmembrane domains insert into sodium dodecyl sulfate (SDS) micelles and fold into α -helices as a result of the hydrophobic effect (page 11111, left column, 2nd paragraph). Melnyk teaches that while micelle-inserted Tar-1 segment migrated as a homodimer on SDS-PAGE, micelle-inserted Tar-2 segment migrated as monomer on SDS-PAGE (page 11111, left column, 3rd paragraph). Melnyk clearly establishes that the Tar-1 helix is the oligomeric determinant for the Tar protein (abstract of Melnyk, page 11111, right column, 1st paragraph). According to Melnyk, helix-helix packing of Tar-1 segments results in the formation of an aspartate receptor homodimer (page 11111, right column, 2nd paragraph). Melnyk does not disclose diastereomeric peptides corresponding to a transmembrane domain of aspartate receptor.

The secondary references of Bolognesi and Gerber do not remedy the above-noted deficiencies of Melnyk.

Bolognesi discloses peptides which exhibit antiviral activity (abstract of Bolognesi). Bolognesi discloses DP-178 truncated peptides and analogs thereof (col. 5, line 19 through col. 7, line 21). Bolognesi further discloses DP-178 peptides comprising at least one amino acid in the D-configuration (see page 10, lines 26-29 of Bolognesi). However, Bolognesi does not provide any example of DP-178 peptides comprising at least one D-amino acid, nor does Bolognesi disclose antiviral activity. One would expect, according to Melnyk, that incorporation of D-amino acids into a peptide corresponding to a transmembrane domain of a membrane protein would affect its helix-helix recognition. However, Bolognesi is silent of such teaching.

Gerber discloses all D-amino acid glycoporphin A (GPA) transmembrane domain and two all-D mutants of GPA transmembrane domain (abstract of Gerber). Gerber further discloses that all D-amino acid GPA transmembrane domain associated with an all-L GPA transmembrane domain within the membrane milieu of E.coli, and concluded that helix-helix recognition within the membrane is chirality-independent (abstract of Gerber).

Thus, according to Melnyk and Gerber, helix-helix recognition is required for transmembrane domains interactions. While the chirality of the helix is not important, the helix structure should be preserved as to maintain the original interactions between the transmembrane domains (abstract of Gerber).

Bolognesi does not provide any teaching for the consequences of replacing L-amino acids with D-amino acids in DP-178.

Thus, even if Melnyk, Bolognesi, and Gerber were combined, one would not expect to obtain membrane binding diastereomeric peptide of the claims corresponding to a transmembrane domain of a transmembrane protein that are active in inhibiting membrane protein assembly. In other words, the combination of Melnyk, Bolognesi, and Gerber is not predictive of the claimed peptide.

It should be noted that the present application clearly discloses that incorporation of D-amino acid residues into the N-terminal part of DP-178 rendered the peptide inactive in inhibiting membrane fusion (page 25, lines 11-12 of WO 2005/060350). On the other hand, incorporation of D-amino acid residues into the C-terminal part of DP-178 did not abolish the inhibitory effect of the peptide on membrane fusion (page 25, lines 10-11 of WO 2005/060350). The present

case thus unexpectedly demonstrates that one can replace L-amino acids with D-amino acids in a peptide which corresponds to a transmembrane domain of a membrane protein without damaging its interaction with the membrane protein as the recognition between the peptide and the membrane protein within the membrane milieu is not dependent on the secondary structure of the peptide (page 4, lines 17- 22 of WO 2005/060350. This is not the case for a peptide which corresponds to an extramembranal domain of a membrane protein where the interaction of the peptide with the membrane protein occurs in aqueous solution and the coiled-coil recognition is essential (page 24, lines 25-32 of WO 2005/060350).

Thus, even if one combines Melnyk, Bolognesi and Gerber, one would not be motivated to incorporate D-amino acid isomers into the peptide of Melnyk as this replacement would abrogate the helix structure of the peptide and hence would damage its activity. In order to clearly define the diastereomeric peptides of the present application, claim 1 has been amended to recite that the diastereomeric peptide corresponds to a transmembrane domain of a membrane protein.

Further, based on the discussion above, it is believed that the claimed peptides exhibit surprising and unexpected properties indicative of non-obviousness. As discussed above, the present case unexpectedly demonstrates

that one can replace L-amino acids with D-amino acids in a peptide which corresponds to a transmembrane domain of a membrane protein without damaging its interaction with the membrane protein as the recognition between the peptide and the membrane protein within the membrane milieu is not dependent on the secondary structure of the peptide. It is well established that rebuttal evidence may include evidence that the claimed invention yields unexpectedly improved properties or properties not present in the prior art. Such evidence may consist of a showing that the claimed compound possesses unexpected properties. *Dillon*, 919 F.2d 688, 692-93, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990).

For these reasons, Applicant respectfully submit that claim 1 as amended, clearly defines a novel and patentable invention over the combination of Melnyk, Bolognesi and Gerber. Thus, the above-noted obviousness rejection over Melnyk, Bolognesi and Gerber is untenable and should be withdrawn.

On pages 21-23, claims 18-21 were rejected under 35 U.S.C. 103(a) as being obvious over Sal-Man et al., JMB 344: 855-864, 2004 (referred to hereafter as "Sal-Man") and Science web page and Bolognesi.

The Examiner stated that claims 18-21 have been searched on a priority date of 12/22/04 as indicated above (page 2 of this letter). The Examiner further stated that Sal-Man teaches peptides of the transmembrane domain of the E. coli aspartate receptor, specifically the peptide KKKMVLGVFALLQLISGSLKKK (Tar-1) in which the peptide is either all L or all D amino acids. Sal-Man does not expressly teach a 'diastereomeric peptide'. The Examiner further stated that Bolognesi teaches peptides which correspond to an HIV transmembrane protein, and specifically teaches the incorporation of at least one amino acid residue in a D-isomer configuration. This rejection is traversed.

Applicant respectfully disagrees with the Examiner's position as to the priority date of these claims. The arguments set forth in section III above are reiterated herein. Based on such, Applicant believes that Sal-Man cannot be regarded as a prior art for claims 18-21, and therefore the combination of Sal-Man and Bolognesi cannot be used to reject these claims for obviousness under 35 U.S.C. 103(a). Thus, the rejection is untenable and should be withdrawn.

X. Conclusion

Having addressed all the outstanding issues, this paper is believed to be fully responsive to the Office Action.

Appln. No. 10/583,996
Reply dated July 10, 2009
Reply to Office Action of April 10, 2009

It is respectfully submitted that the claims are in condition
for allowance and favorable action thereon is requested.

If the Examiner has any comments or proposals for
expediting prosecution, please contact the undersigned.

Respectfully submitted,

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